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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,667	09/28/2001	Suzanne De La Monte	0609.4370005/RWE/FRC	3648

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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,667	DE LA MONTE ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

SMC

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-52* is/are pending in the application.

4a) Of the above claim(s) *46-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I, claims 35-42 and SEQ ID NO: 9 in the reply filed on 2/27/04 is acknowledged. Upon reconsideration the examiner has rejoined claims 43-45 with the elected invention for examination. Claims 35-45 and SEQ ID NO: 9 are under examination.

Claims 46-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/24/04.

Claims 35-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to the treatment or prevention of neuroectodermal tumors, malignant astrocytomas and glioblastomas via the administration of an assortment of antisense based nucleic acid based compounds. The compounds are antisense and ribozymes which correspond to a sequence of NTP mRNA defined by nucleotides 150-1139 of SEQ ID NO: 1 and specifically SEQ ID NO: 9.

The instant specification as filed provides only general guidance for the various antisense based nucleic acid compounds used in the claimed method. The specification

provides general methodologies for determining effective sequences for the nucleic acid compounds used in the method and provides general methods for delivery of compounds in a treatment, for example (see pages 24-33). Example 8 of the specification shows that the recombinant over expression of AD7c-NTP in cells in culture produces phenotypes associated with Alzheimer's disease neurodegeneration (see page 46, for example). It is noted that it is not clear what particular AD7c-NTP was used in the example since "AD7c-NTP" is defined by the instant specification to include variants (see page 17, for example). The specification states at page 18 that because AD7c-NTP is associated with Alzheimer's disease it can be used to screen for drugs to treat neuroectodermal tumors, malignant astrocytomas and glioblastomas. The specification provides no guidance for the treatment of the above diseases via antisense based nucleic acid compounds. The claimed invention reads on the prevention of cancer, for example where the specification provides no guidance on how one in the art would prevent a cancer from occurring.

The instant specification does not provide any specific guidance such as what particular antisense or ribozyme could be used effectively in the claimed method. The instant specification does not provide guidance or examples that would show by correlation what sequences of antisense based nucleic acid compounds of the method would predictably provide for treatment or prevention of disease in general or for the treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas specifically. The instant specification does not provide guidance or examples that would show by correlation what modes of delivery would predictable provide for a treatment of

disease in general and for the treatment or prevention of neuroectodermal tumors, malignant astrocytomas and glioblastomas in particular. The instant specification does not provide any examples of inhibiting AD7c-NTP in cells in culture or in an animal or provide guidance that would show by correlation the treatment or prevention of neuroectodermal tumors, malignant astrocytomas and glioblastomas via the administration of antisense based nucleic acid compounds. The specification provides a system that may screen for compounds that may inhibit AD7c-NTP, but the specification has failed to provide one in the art a means to predictably make a nucleic acid based compound used in the claimed method of treatment or prevention such that no undue experimentation would be required in the making of the compound (ie selection of a predictable effective [in vivo] sequence) and further how to deliver such a compound in a whole animal such that one would be able to treat or prevent neuroectodermal tumors, malignant astrocytomas and glioblastomas without undue trial and error experimentation. The art of nucleic acid based therapies in an unpredictable art. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides {The instant specification fails to provide any guidance or

examples that show an uptake of nucleic acid compound that would correlate to a predictable treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas, for example}. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). The instant specification fails to consider the problems asserted above, for example. The specification fails to provide any particular guidance on how to deliver adequate oligonucleotiodes to a specified target cell such that there is a treatment or prevention of the recited diseases.

Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability

confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is

beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

It is clear from the reference above that the art of antisense based therapy is an unpredictable art where the determination of effective sequences and modes of delivery are clearly not routine where one in the art requires specific guidance for any antisense based treatment of any particular disease, for example. One in the art would be required to engage in undue trial and error experimentation to practice the claimed invention since the specification as filed has failed to provide any particular sequences of the various antisense based compounds recited in the claim that would predictably be

effective in the treatment or prevention of d neuroectodermal tumors, malignant astrocytomas and glioblastomas and also fails to provide with any particularity how one would specifically treat neuroectodermal tumors, malignant astrocytomas and glioblastomas with antisense based nucleic acid compounds. One in the art is left to trial and eror experimentation to practice the claimed invention.

Applicant's arguments filed 11/07/03 have been fully considered but they are not persuasive. Applicant argues that the general disclosure of antisense methodologies of the specification is sufficient to enable the full scope of the claimed invention since the particularities of antisense based therapy would have been available to one in the art at the time of invention. Applicant asserts that it is the burden of the examiner to set forth a reasonable basis to question the enablement provided for the claimed invention. The rejection of record is believed to provide the required reasonable arguments and evidence. Applicant argues at page 10 that a skilled artisen would appreciate that antisense based compounds function by recognizing complementary or corresponding nucleotide sequences to inhibit translation or transcription. This is part of the process since one would need to deliver a sufficient amount of such antisense based compounds to a particular target cell and further be assured that the antisense will find the targeted region accessible in the environment of required action. A treatmnent of prevention of a particular disease requires more than the esblishment that an antisense oligonucleotide may have the capacity to inhibit a target gene but also includes the determination that the capacity is realized in the therapeutic (in vivo) setting and also a

mode to provide a sufficient amount to the required cells or tissues. Applicant argues at page 11 "that any mode of delivery that brings the compounds in contact with neuronal cell in an animal would be effective". This statement lacks any guidance for just what those modes might be for any particular treatment or prevention, for example. Applicant has provided a reference Galderisi et al as evidence that the art was sufficiently advanced at the time of filing such that no particular guidance would be required to be given in the specification for the claimed method. The evidence and applicant arguments are not agreed with. It is noted that the Galderisi et al reference provides examples of some success in the art in the application of antisense in the treatment of disease. It is not disputed that antisense may be used in treatment of disease, but the amount of guidance required to perform such treatment without undue trial and error experimentation in view of the state of the art is high. Applicant has argues particularities of the cited references, but it is clear when the references are taken as a whole that the state of the art of therapy via antisense is an unpredictable art. Even the reference [Galderisi] cited by applicant concludes "the use of antisense to modify gene expression is variable in both its efficacy and reliability. . . . [m]ost of these concerns can be overcome by the development of a new generation of antisense molecules with improved target specificity and enhanced delivery to the target cells. The rejection of record is therefore maintained for the same reasons of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
Primary Examiner
Art Unit 1635

SRM